Subclinical Hypothyroidism In Women: Will Screening And Early Detection Reduce Hyperlipidemia?

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Citation

A Olson. *Subclinical Hypothyroidism In Women: Will Screening And Early Detection Reduce Hyperlipidemia?*. The Internet Journal of Advanced Nursing Practice. 2000 Volume 5 Number 1.

Abstract

Hypothyroidism, a progressive disorder of the thyroid gland, is a common condition affecting more women than men. The prevalence of age-related hypothyroidism in women is well documented. Associated hyperlipidemia is common especially in the clinical presence of positive serum antithyroid antibodies. The relationship between subclinical hypothyroidism (SH) and hyperlipidemia among women is less well known. Although as many as 24% of elderly women with SH will progress to overt hypothyroidism, routine screening for thyroid dysfunction is not widely accepted among health care professionals and organizations.

This article will review the literature on SH in women in relation to serum lipid concentrations and associated pathology. Clinical guidelines and an algorithm for screening and managing SH in view of hyperlipidemia will be suggested.

INTRODUCTION

Hypothyroidism is a progressive metabolic disorder of many causes in which the thyroid gland fails to secrete an adequate quantity of thyroid hormone. The majority of cases are due to primary thyroid failure in chronic autoimmune Hashimoto's thyroiditis, from radioactive iodine therapy, or from thyroid surgery ([1]). Secondary causes of hypothyroidism are usually due to conditions that interfere with normal pituitary-hypothalamic function such as a pituitary adenoma ([2]). Elevated serum TSH and low free T4 levels determine the diagnosis of hypothyroidism. Common clinical presentations of hypothyroidism, as presented in the Billewicz index, are listed in Table 1 (1, 2, [4]). Subclinical hypothyroidism (SH) is typically defined as asymptomatic, characterized by slightly increased serum TSH levels and normal serum T4 concentrations (1, 2, [5], [6]). Some studies suggest that similar but milder symptoms of hypothyroidism are present in SH ([7], [8]).

Figure 1

Table 1. Clinical Signs and Symptoms Associated with Hypothyroidism

Skin Changes:	**Exam Findings:**
Decreased sweating response	Decreased hearing, deafness
Coarse texture	Pulse rate < 75 bpm
Coldness	Delayed Achilles' tendon reflex
Dryness	Muscle weakness
Changes in body:	
Increased weight	
Constipation	
Periorbital edema	
Hoarse voice	
Slower movements	
Paresthesias	
Intolerance to cold	
Menstrual changes	

HOW COMMON IS SUBCLINICAL HYPOTHYROIDISM?

Reported prevalence of SH in literature varies. According to the 1996 Report of the U.S. Preventive Services Task Force, SH is found in 6-8% of adult females and 3% of adult males, with approximately 20-24% of elderly SH patients testing positive for thyroid antibodies eventually developing overt hypothyroidism within several years. SH becomes more prevalent with age ([9], [10], [11]). SH is common among middle-aged women most often after menopause, as indicated by an associated increased prevalence of serum antibodies thought to be directed toward a microsomal antigen labeled thyroid

peroxidase (7). For purposes of this article, the diagnosis of SH is defined as a TSH level of >4.0 mU/L with a normal free T4 level unless otherwise specified (7, 8, [12]).

According to the Whickham Survey (11) in which a random sample of 2779 adults were observed for thyroid disease over a 20-year period, an increased risk for hypothyroidism among women was found. In this long-term study, the annual risk among women of developing hypothyroidism was 4.3% per year if both an elevated serum TSH and anti-thyroid antibodies were found, 2.6% with elevated TSH alone, and 2.1% per year with positive anti-thyroid antibodies alone. The study also demonstrated that, independent of age, the higher the serum TSH level is above 2 mU/L, the greater is the likelihood of developing overt hypothyroidism with or without anti-thyroid antibodies.

GUIDELINES FOR SCREENING: CONTROVERSIAL

A detailed medical history and physical examination may reveal signs and symptoms of previously undiagnosed hypothyroidism. Hypothyroidism may be associated with a normal size thyroid gland, or with the presence of a goiter that may need surgical evaluation. For purposes of this article hypothyroidism and SH will be discussed in the context of thyroid disease without goiter.

The most commonly used thyroid function tests for primary hypothyroidism include the following:

- Thyroid stimulating hormone (TSH) measures the concentration of serum thyroid stimulating hormone, which is under negative feedback control as a result of free thyroid hormone (T4 and T3) and under positive control by the hypothalamic thyroid releasing hormone. Although the specific range for a normal TSH may vary among clinical pathology labs, the average TSH in most individuals is between 0.3 and 5.0 mU/L (13). The TSH is the most widely used test with high specificity and sensitivity for hypothyroidism (4).
- Free T4 (FT4) measures the concentration of free thyroxine, the biologically active serum thyroid fraction. The FT4 is not affected by alterations in the serum concentration of binding proteins as thyroid-binding globulin or thyroid binding prealbumin, and is the most reliable measurement of circulating thyroid hormone (2).
- Total T3 (T3) measures the concentration of serum triiodothyronine. In hypothyroidism the T3 is usually normal despite a low T4, and is decreased during acute illness and malnourishment. Routine measurement of T3 is usually not indicated due to the poor correlation with thyroid status (2).
- Antithyroid antibodies are associated with thyroid disease and are the antithyroid microsomal (measured by the antithyroid peroxidase assay), the antithyroglobulin and the thyroid simulating immunoglobulin. The antibodies attach to the thyroid gland's thyrotropin receptor and activate it. The presence of elevated serum levels of thyroid antibodies is thought to contribute to eventual overt hypothyroidism (11).

Table 2 (6, [14]) lists clinical situations when screening for hypothyroidism may be considered.

Figure 2

Table 2. Clinical Factors Associated with Hypothyroidism

Family History	**Clinical Presentation**
Autoimmune disease	Presence of antithyroid antibodies
Type I diabetes	Sleep apnea
Addison's disease	Unexplained weight loss
Autoimmune thyroid disease	Abnormal lab values
	Hypercholesterolemia
	Hyponatremia
	Anemia
Medical History	Elevated creatine phosphokinase
Head or neck surgery	Elevated lactate dehydrogenase
Postpartum thyroiditis	Hyperprolactinemia
Thyroid disease or goiter	
Heart disease	
Chromosomal abnormalities	
Psychiatric disease	
History of medication use:	
Amiodarone	
Lithium	
Interferon	
Iodine-containing substances	

The use of the sensitive TSH has benefited researchers and practitioners in identifying patients with abnormal thyroid function before clinical symptoms or other laboratory abnormalities present. At present, no widely accepted clinical guidelines recommend routine screening for thyroid disease in the absence of symptoms. Screening for thyroid disease in newborns is a mandatory practice supported by major health organizations. The following are organizations with statements regarding routine screening for thyroid disease.

- The American Thyroid Association set minimum standard guidelines for primary care practitioners in the evaluation of patients with symptoms of and with known thyroid disorders believing that cost

savings and efficient care would be achieved. Screening is suggested for women beginning at age 35 and at subsequent 5-year intervals, for individuals with a strong family history of thyroid disease, the elderly, women at 4-8 weeks postpartum, and patients with autoimmune illnesses (1, 14).

- The U.S. Preventive Services Task Force does not recommend routine screening of asymptomatic patients of any age. Clinicians are encouraged to evaluate patients with subtle signs and symptoms of thyroid disease (15).
- The American College of Physicians presented guidelines in 1998 for screening of thyroid disease within the primary care setting. A serum TSH is recommended in women over age 50, but not in younger women or in men due to the low prevalence of asymptomatic thyroid disease in these groups. Evidence was insufficient to support recommendations for or against the treatment of SH in patients with mildly elevated TSH levels. A suggestion was to treat symptomatic patients or those with hyperlipidemia. Clinical follow-up every 2 to 5 years was recommended (16).

Sadovsky, in his review article, noted that patients with SH based on serum TSH levels of >5.0 with a normal free T4 level, are at risk for hypercholesterolemia and eventual overt hypothyroidism. Further stated is the uncertainty of treatment effectiveness, however clinical follow-up of patients with TSH levels between 5.0-10.0 mU/L is recommended. Clinicians are encouraged to consider thyroid replacement therapy in patients with a serum TSH of >10.0 or with positive antithyroid antibodies (13).

THYROID HORMONE REPLACEMENT THERAPY IN HYPOTHYROIDISM

Patients diagnosed with hypothyroidism clearly benefit from therapy with thyroid replacement. Treatment is to be introduced slowly due to individualized response to thyroid hormone effects as high replacement rate may cause nervousness, palpitations and mild tremor. Therapy is to be lifelong, except in transient hypothyroidism as in subacute or postpartum thyroiditis (2).

Levothyroxine, available in various dosages that allow individualized titration, continues to be the most recommended source of thyroid replacement (1, 2). In women younger than age 50 years, the starting dose may be 1.7 mcg/kg of body weight or 0.112 mg daily and adjusted after 6-8 weeks when the daily dose may be increased by 0.0125 to 0.025 mg (6). Women over 50 years may begin at a dose between 0.025 to 0.050 mg daily with gradual levothyroxine doses titrated as in younger women. Levothyroxine should be taken at least four hours apart from other medications such as anticonvulsants, rifampin, iron compounds, cholestyramine, sucralfate, and aluminum hydroxide antacids (1, 6).

Ongoing clinical monitoring is recommended to evaluate the therapeutic and possible adverse response to treatment, medication compliance, and to adjust any dosage due to health changes. If dosages are adjusted, a follow-up evaluation in 8 weeks is recommended to re-evaluate serum TSH concentration and clinical response to therapy. When the TSH is normalized, clinical evaluations may be done annually.

Therapy for SH is controversial, but is suggested in the presence of antithyroid antibodies with or without hypothyroid symptoms, due to the high frequency of eventual overt hypothyroidism (1, $_{3}$).

COMPLICATIONS OF SH ON FUTURE CARDIOVASCULAR HEALTH AND QUALITY OF LIFE

The possible complications of SH are symptoms, hyperlipidemia and eventual overt hypothyroidism (8, 10, 12). Research has suggested a relationship between hypothyroidism and hypercholesterolemia and subsequent cardiovascular disease (5, 6, 10, 12, 16). Hemodynamic changes associated with hypothyroidism include increased vascular resistance, decreased tissue perfusion, and a decreased peripheral oxygen consumption (16). Whether SH is also a primary risk factor for cardiovascular disease is unproven, though case-control and cross-sectional studies have been done (5, $_{17}$).

In the Rotterdam Study (12), 4878 women aged 55 or older were evaluated for chronic disease occurrence and relative predisposing factors. A cohort random sampling of 1149 women was obtained to study if SH and thyroid autoimmunity were risk factors for cardiovascular disease. When TSH levels were greater than 4.0 mU/L, serum free T4 levels were also measured. Adjusting the study for body mass index, HDL and total cholesterol, blood pressure and smoking status, the researchers found SH in 10.8% of participants and relative increased risks for myocardial

infarction (odds ratio 2.3, [CI, 1.3 to 4.0]) and aortic atherosclerosis (odds ratio 1.7, [95% CI, 1.1 to 2.6]) compared to euthyroid controls. Further evaluation revealed that SH participants with positive antibodies to thyroid peroxidase had slightly increased risks for both atherosclerosis and myocardial infarction.

A randomly chosen group of 427 women aged 40-60 years (mean age 55 years) were studied to determine the relationship between serum TSH and antithyroid antibody levels in regard to thyroid disease; lipid profiles of participants with elevated serum TSH levels were studied ten years after the initial survey ([18]). The prevalence of SH was 4% initially and 7.3% after 10 years (95% CI 2.1-5.9% and 4.8-9.8%). The prevalence of patients with positive serum antithyroid antibody levels was 11% (CI 8.3-14.1) with 39.6% of the antithyroid antibody-positive group and only 3.2% of the antithyroid antibody-negative group developing elevated serum TSH levels during the 10-year study (P<0.01). The results of this study did not show an increased incidence of hypercholesterolemia among women with elevated serum TSH levels as compared to controls at the end of the study, however women with positive antithyroid antibodies and elevated serum TSH levels were not separated in the final analysis of lipid profile effects.

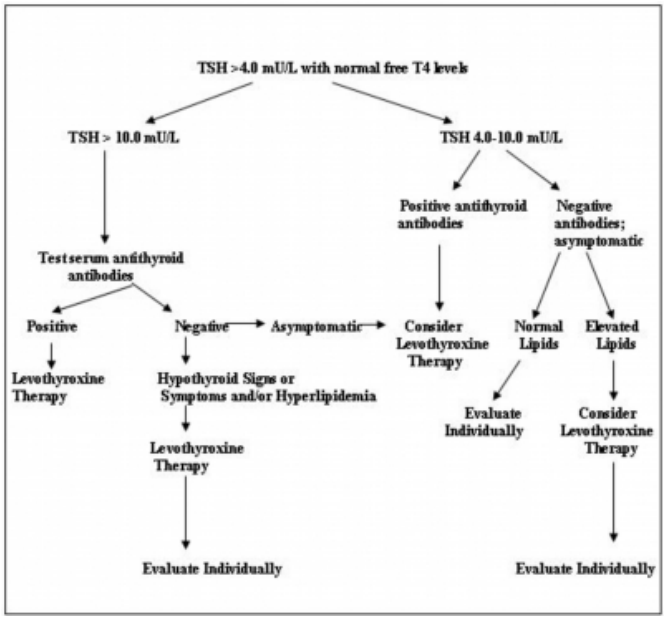
The authors suggested that testing for antithyroid antibodies in women over 40 may offer further clinical information in the prevention of overt hypothyroidism and subsequent cardiovascular disease as women age.

Tanis, Westendorp and Smelt ([19]) reviewed 148 studies that used thyroid hormone replacement as intervention in SH patients with hypercholesterolemia. In their review, patients with hypercholesterolemia were two to three times more likely to have SH. Also, patients with SH were found to have slightly higher levels of serum total cholesterol.

Table 3 offers a suggested clinical plan for screening women for SH and potentially associated hyperlipidemia using the suggested guidelines and related research (1, 3, 13, 14).

Figure 3

Table 3. Algorithm for SH Screening and Potential Treatment



CRITERIA FOR CLINICAL SCREENING

Helfand and Redfern (8) suggest these criteria for screening in the following clinical situations:

- An abnormal lab test is associated with expected complications that compromise future health and quality of life.
- Clinical follow-up and early treatment will reduce risks for these complications.
- Benefits of follow-up and treatment are greater than risks.

IS CLINICAL FOLLOW-UP AND EARLY INTERVENTION BENEFICIAL?

Hyperlipidemia is known to be a risk factor in cardiovascular disease. Hypothyroidism is thought to increase the risk of hyperlipidemia. Will serum lipid levels decrease in SH patients with hypercholesterolemia who are treated with thyroid hormone?

Tanis et al (19) in their multi-studies review stated that substitution of thyroid hormone in patients with SH and hypercholesterolemia reduced total serum cholesterol levels by an average of 6%. Considerations noted in their review of these intervention studies are:

- An overestimation of the effect of thyroid

substitution on the lipid profile may have been affected by dose oversubstitution resulting in TSH levels falling to below normal, however in most of the studies, the dose was titrated to achieve a euthyroid state.

- An underestimation of the effect of thyroid substitution on the lipid profile may have been affected by the short duration of treatment in some studies, although in most of the studies patients were treated for longer than four weeks.

Staub et al (10) observed 86 women, ages 49-55, with SH (n=69), with overt hypothyroidism (n=17) and with euthyroid women (n=52) as controls. All women underwent similar clinical screening including serum TSH, free T4, T3, thyroid antibodies and lipid profiles. This study further categorized all hypothyroid patients into five areas according to severity of thyroid disease:

- Grade I: TSH < 6.0 mU/L, normal free T4 and T3, history of thyroid disease (n=35)
- Grade II: TSH 6.0 to 12.0 mU/L, normal free T4 and T3 (n=14)
- Grade III: TSH > 12.0, normal free T4 and T3 (n=20)
- Grade IV: TSH > 20.0, elevated T4, normal T3 (n=7)
- Grade V: TSH > 20.0, elevated T4, decreased T3 (n=10).

Results demonstrated that elevated serum LDL cholesterol levels were found in 42.9% of patients with Grade III disease compared with 11.4% of control group patients. There were no differences in the five subgroups. Cohort analysis of lipid data for premenopausal women did not affect the results significantly. Limitations of this investigation include small numbers studied overall as well as in each subcategory, and the lack of a clinical definition of premenopausal status.

IS SH FOLLOW-UP AND TREATMENT BENEFICIAL?

Although the benefits of treatment for hypothyroidism are well-established, comparable benefits of treatment for SH remains controversial. Some studies suggest that clinical follow-up and treatment of SH may decrease hypercholesterolemia and subsequently reduce risk for cardiovascular disease (8, 9, 19).

Estimates from Helfand and Redfern's meta-analysis of studies of thyroid dysfunction screening and treatment of SH complications showed that although treatment may not always be indicated, women over age 50 may benefit from thyroid screening (8). Their finding suggested that patients with a TSH of > 10.0 mU/L would be most likely to benefit from early treatment. Treatment was estimated to reduce serum cholesterol levels by an average of 8% in these same patients with existing hyperlipidemia. One in approximately every 250 patients were predicted to benefit, further suggesting that if therapy were effective in reducing hyperlipidemia, 1 incident of coronary artery disease would be prevented in every 95-200 patients treated for 5 years.

Benefits of early treatment need to be balanced with the potential disadvantages. Thyroid replacement therapy is considered to be long-term, therefore pharmaceutical and clinical screening costs are to be considered. Potential health considerations of long-term therapy are subclinical hyperthyroidism that may occur if the TSH remains below normal range. Women on long-term thyroid replacement therapy may be at risk for decreased bone density and may need bone density screening begun at earlier ages. Over-medicating with thyroid replacement may be related to cardiac function alteration and some neuropsychological symptoms (3).

Large randomized trials are needed to further evaluate whether routine screening and subsequent treatment of women with SH will improve quality of life and/or decrease cardiovascular disease risks.

CONCLUSIONS

Hypothyroidism is a condition of significant health consequences with associated hyperlipidemia well documented. Prevalence among women increases with age. Subclinical hypothyroidism is less well defined clinically. The risk of developing overt hypothyroidism and subsequent cardiovascular health risks among patients with SH is to be considered.

Nurse practitioners and other health care providers are encouraged to screen women age 40 years or older who have hypercholesteroleremia with serum TSH, free T4 and thyroid antibodies. The decrease in serum total cholesterol that may be reached through thyroid hormone replacement in these

patients may be a possible adjunct in risk management for cardiovascular disease. Clinicians may prescribe individualized treatment with thyroid hormone replacement according to the patient's overall risk status and continue clinical evaluations as indicated. The benefits and risks of long-term thyroid hormone replacement in women with SH and hyperlipidemia needs to be evaluated in larger clinical trials.

Further studies are also needed before clinicians can recommend treatment for all women with SH. If clinical observation is chosen instead of treatment, the nurse practitioner is encouraged to include serum lipid analysis, serum thyroid function tests and should observe for progression toward overt hypothyroidism during annual clinical evaluations.

ALL REQUESTS TO BE SUBMITTED TO

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